

Accuracy of a Flash Glucose Monitoring System in Diabetic Dogs

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Background: A novel flash glucose monitoring system (FGMS) (FreeStyle Libre, Abbott, UK) was recently developed for humans. It continuously measures the interstitial glucose (IG) concentrations for 14 days.

Objectives: To assess the clinical and analytical accuracy of the FGMS in diabetic dogs.

Animals: Ten client-owned diabetic dogs on insulin treatment.

Methods: Prospective and observational study. The FGMS was placed on the neck for up to 14 days. During the 1st–2nd, 6–7th, and 13–14th days from application, the IG measurements were compared with the plasma (EDTA) glucose (PG) concentrations analyzed by a reference hexokinase based method.

Results: The application and the use of the FGMS were apparently painless, easy, and well tolerated by all dogs. Mild erythema at the site of the application was found in 5/10 dogs at the end of the wearing period. A good correlation between IG and PG concentrations ($\rho = 0.94$; $P < .001$) was found. The FGMS was 93, 99, and 99% accurate at low, normal, and high blood glucose concentrations. Mean \pm standard deviation difference from the reference method was 2.3 ± 46.8 mg/dL.

Conclusion and clinical importance: The FGMS is easy to use and is accurate for IG glucose measurement in diabetic dogs.

Key words: Canine; Diabetes mellitus; FreeStyle Libre; Noninvasive glucose measurement.

Glycemic control is a cornerstone for the management of diabetes mellitus (DM) in human and veterinary medicine. Self-monitoring blood glucose system and continuous glucose monitoring systems (CGMS) are routinely used in human diabetic patients. Different systems for real-time CGMS have been available for the use in human diabetic patients and many publications support the clinical benefit of the CGMS.¹

In diabetic dogs, the evaluation of blood glucose curves (BGCs) allows the clinician to determine if the insulin administered is effective and identify the glucose nadir, time of peak insulin effect, duration of insulin effect, and degree of fluctuation in blood glucose concentrations in that particular dog. To perform a BGC, the diabetic dog is generally hospitalized for 10–12 hours and the capillary blood glucose concentration is usually measured every 2 hours. Nowadays, some

Abbreviations:

CGMS	continuous glucose monitoring system
FGMS	flash glucose monitoring system
IG	interstitial glucose
PBGM	portable blood glucose meter
PG	peripheral blood glucose

owners are able to perform home monitoring by measuring the capillary blood glucose concentrations using a portable blood glucose meter (PBGM). The main limitations of the BGCs interpretation include the requirement of numerous capillary drops of blood that in some dogs can be difficult to obtain and become a source of stress; nevertheless, the glucose nadir or peak can be missed measuring the blood glucose concentration every 2 hours. Moreover, the BGCs in the hospital are time consuming and expensive.

The use of CGMS has been already described in veterinary medicine,^{2–9} even though the devices used in previous studies have a number of limitations and are not commonly used clinically. The CGMS can measure the IG concentrations in the subcutaneous interstitial fluid. Such devices typically consist of a sensor that is applied on the surface of the body to measure glucose concentrations and a transmitter by which the glucose data are displayed. The first generation systems offered only retrospective analysis of the glucose concentrations after disconnecting the sensor and uploading the data, whereas the newest generation measure and display the data immediately, allowing direct intervention (real-time CGMS).¹⁰ However, the main shortcoming of most CGMSs is that they need to be calibrated and therefore capillary blood sampling is required.^{9,10}

A novel flash glucose monitoring system (FGMS^a) has been licensed recently for the use in the European Union (CE mark August 2014). The FGMS measures interstitial tissue (IG) glucose levels every minute via a disposable round sensor with a small catheter inserted

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under the skin that can be worn for up to 14 days. This FGMS is factory-calibrated and does not require finger-stick blood glucose measurements for calibration. It is designed for human diabetic patients to replace blood glucose monitoring and for use in day-to-day treatment decisions.

The present study evaluates the analytical and clinical accuracy of the FGMS in diabetic dogs.

Materials and Methods

Dogs

Ten client-owned diabetic dogs were enrolled in the study. All dogs were diagnosed with DM and they were on insulin treatment for at least 1 month. Seven were neutered females and 3 were males (2 castrated). Breeds included mixed breed (4 dogs), Dachsbracke (1), English Setter (1), Epagneul Breton (1), Toy Poodle (1), Springer Spaniel (1), and Yugoslavian Shepherd dog (1). The median age was 9.5 years (range 2–13) and the median body weight was 18.0 kg (5.4–43.0 kg). Seven dogs were treated with porcine insulin zinc suspension,^b 2 with glargine,^c and 1 with Neutral Protamine Hagedorn (NPH) human analog insulin.^d All dogs did not have any concurrent disease and did not receive any other drugs during the study period. The protocol and informed consent forms were approved by the Scientific Ethics Committee of the University of Bologna. The recruitment of dogs in the study was voluntary and at no cost to the owners. Written informed consent before enrollment in the study was obtained.

Flash Glucose Monitoring System

The flash glucose monitoring system,^a FreeStyle Libre is composed of a small round sensor (35 mm × 5 mm). The sensor has a small catheter (0.4 mm × 5 mm) inserted under the skin through which the sensor can measure the IG concentration. It can be worn for up to 14 days and is water resistant. The sensor is applied on the skin easily and intuitively by the applicator furnished by the manufacturer.

The sensor is based on the glucose-oxidase method, which measures an electrical current proportional to the glucose concentration. The electrode has a long carbon chain that holds both glucose oxidase and an osmium mediator, called a “wired enzyme”. After glucose has reduced by the glucose oxidase, the

enzyme passes its electrons to the osmium mediator rather than oxygen. The mediator then passes the electrons to the electrode for measurement, this avoids using oxygen and thus the requirement for a limiting membrane on the sensor.^{11,12} The detection limits of the sensor are between 20 and 500 mg/dL; however, the readings beyond this range are not recorded. The system starts working 1 hour from application (Fig 1).

This system is factory calibrated, so it does not require any calibration before and during the wearing period. Measuring blood glucose and correlating it to the sensor current at one point in time determines the calibration factor. The sensor has to be scanned by the reader and in 1 second the reader can show instantaneously the glucose reading. The FGMS generates information every minute and the readings, day and night, are collected, registered, and stored automatically. An USB port on the reader can be used to charge it and to download all data on a computer. The software used by the FGMS generates different reports from the uploaded sensor data. Moreover, the reader contains a port that can be used with a test strip for built-in blood glucose and ketone meters. At the end of wearing period, the sensor is fully disposable but the reader can be re-used for a new sensor. In this study, a single sensor was placed in a clipped and sterile area (5 cm × 5 cm) on the neck of each diabetic dog (Fig 2A). After positioning, the sensor was fixed with extra tape and a body bandage was used to secure the sensor at the body (Fig 2B–C). At the end of wearing period all dogs were judged subjectively for the presence of erythema by the same clinician (SC).

Accuracy of FGMS

To compare the glucose readings measured with FGMS to the reference method (hexokinase method), paired samples were collected and then classified in the hypoglycemic (<70 mg/dL), in the euglycemic range (70–180 mg/dL), and in the hyperglycemic range (>180 mg/dL). All the values above and below the detection limit of the sensor (≤20 and ≥500 mg/dL) were excluded (Fig 3).

During the wearing period of the sensor, each dog was evaluated for 3-time periods as follows: from the 1st to 2nd day, from the 6 to 7th, and from the 13 to 14th day. During every evaluation period, that lasts 36 hours, blood samples were collected simultaneously every 2–3 hours from cephalic intravenous catheter previously placed. Mean (SD) number of samples, obtained during the 1st–2nd, 6–7th, 13–14th were 16.5 (12.4), 17.8 (6.5), and 16.6 (4.0) respectively.



Fig 1. FreeStyle Libre FGMS is composed of the following: (A) the reader that in one-second shows the glucose reading; (B) the sensor that with a small catheter measures the interstitial blood glucose in the subcutaneous tissue; and (C) the sensor is applied on the skin by the provided applicator.



Fig 2. (A) The sensor is applied on the neck of the dog; (B) with extra-tape to secure it on the skin surface; and (C) a bandage was used as an additional security.

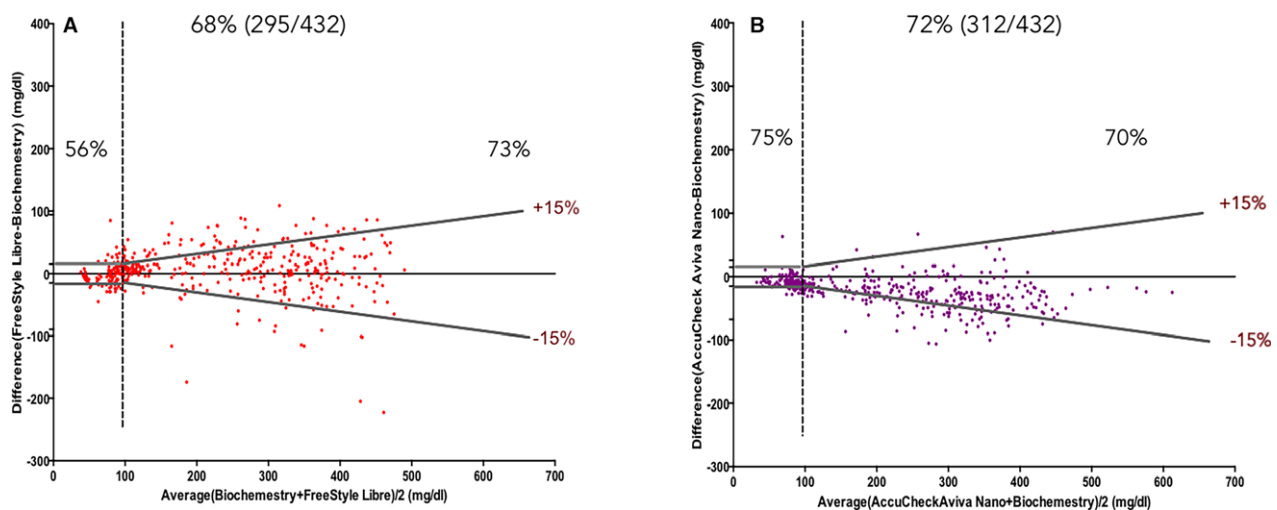


Fig 3. Bland–Altman plots represent the differences between blood glucose concentrations obtained by the use of FGMS versus the reference method (hexokinase). (A) the values obtained by the use of FGMS and the PBGM (Accu-Check Aviva Nano); and (B) including all samples for ISO15197: 2013. On the *x*-axis are, the reference glucose values plotted against the absolute errors for each corresponding value. The standard required limits defined by the gray symmetric lines: at ± 15 mg/dL from the reference value for glucose determinations < 100 mg/dL and at $\pm 15\%$ from the reference for glucose ≥ 100 mg/dL. Percentages express the number of samples within limits when reference was $<$ or ≥ 100 mg/dL and for the total number of measurements (central% value).

During every sampling 0.5 mL of venous whole blood were collected from each dog in a plasma EDTA tube and immediately centrifuged for the analysis of peripheral venous glucose (PG) by the hexokinase method. This was considered the reference method and for this purpose an automated chemistry analyser,^{c,f} routinely monitored with a robust QA program, was used.

Additionally, 0.6 μ L of whole blood were used to measure the glucose with a portable blood glucose meter (PBG), the Accu-Check Aviva NANO,^g a PBGM that has been recently evaluated.¹³ Simultaneously, within 1 minute from the sampling, it also scanned the FreeStyle Libre on the sensor and all data were registered.

The readings of FGMS were compared with those of the hexokinase method used as a reference.

To assess clinical accuracy the ISO 15197:2013 requirements^h were used in accordance with the blood-glucose monitoring system and shall meet both the following minimum criteria for acceptable system accuracy: (1) 95% of the measured glucose values shall fall within either ± 15 mg/dL of the average measured values of the reference measurement procedure at glucose concentrations < 100 mg/dL or within $\pm 15\%$ at glucose concentrations ≥ 100 mg/dL; and

(2) 99% of individual glucose measured values shall fall within zones A and B of the Parkes Consensus Error Grid analysis¹⁴ (Consensus EGA) for type 1 DM. Consensus for the EGA system was performed to assess clinical risks for each measurement and assigned on the *x* axis the values of glucose concentrations measured by the reference method versus the values of glucose concentrations measured by FGMS on the *y* axis to 8 concentric zones with no discontinuities (A through E) defined by different lines.¹⁴

Data Analysis

Normality was assessed with the Shapiro–Wilk test and non-parametric tests were used accordingly.

Correlation between the IG measured by FGMS and PG measured by the hexokinase method was evaluated with Spearman's rank correlation. The differences between IG and the PG were plotted against the reference values in Bland–Altman plots. The differences between the PG measured by the hexokinase method and glucose measured by the PBGM were plotted against the reference values in Bland–Altman plots.

The Friedman 2-way ANOVA was used to compare the differences between IG and the PG in the 3-time periods. The Mann–Whitney test evaluated the interference by the presence of inflammation at the site of application. Statistical analysis was performed with the aid of commercially available software.^{1,j} Differences were considered significant at $P < .05$.

Results

Practical Use of the FGMS

The application and use of the FreeStyle Libre were painless, easy, and well-tolerated by all dogs. In all dogs, the sensor read the IG concentrations after 60 minutes from application. In 7/10 dogs, the sensor lasted for 14 days, although in 3/10 the sensor stopped to record interstitial glucose before the end of the study because it was accidentally detached from the dog's skin. At the end of the study 5/10 dogs showed mild erythema at the site of application of the sensor and 1 dog had bent the needle. The FGMS was able to detect all the interstitial glucose fluctuations (because of insulin treatment and food administration) when they were within the detection limits of the instrument. Rapid changes of glucose concentrations like in the Somogyi effect were not detected during the study.

Accuracy of the FGMS

Four hundred thirty-two paired samples were taken. Based on the reference method (hexokinase), 7% (29/432) of samples were in the hypoglycemic range with a median glucose concentration (min–max) of 54 mg/dL (37–69); 40% (173/432) of samples were in the euglycemic range with a median glucose concentration of 96 mg/dL (72–180); and 53% (230/432) of samples were in the hyperglycemic range with a median glucose concentration of 327 mg/dL (183–625).

Forty percent (173/432) of samples were collected in the first time period, 33% (143/432) of samples were collected in the second time period, and 27% (116/432) during the last time period. Considering all methods, hexokinase, FGMS, and PBGM, the median glucose concentrations (min–max) were 198 mg/dL (37–625), 205 mg/dL (40–495), and 179 mg/dL (28–600) respectively. The median difference (min–max) between the IG measured by the FGMS and hexokinase method was 5 mg/dL (–385–309 mg/dL); instead, the median difference between the PBGM and the hexokinase method was –17 mg/dL (–123–70 mg/dL).

Correlation between the IG measured by the FGMS and the peripheral glucose measured by the exochinase method with $\rho = 0.94$. The correlation coefficient value decreased considering only the samples in the hypoglycemic ($R = 0.43$, $P < .001$), euglycemic ($R = 0.50$, $P = .018$), and hyperglycemic ($R = 0.85$, $P < .001$) ranges. Moreover, the median individual correlation was $\rho = 0.85$ (0.22–0.98). Considering all samples, the mean differences in the glucose concentrations (mean; SD) obtained with the FGMS compared to the reference method and the readings obtained by the PBGM compared to the reference method were 2.3;46.8 and

–21.2;23.7 mg/dL respectively (Fig 3). When evaluating the different glycemic intervals, the mean differences in the glucose concentrations obtained with FGMS compared with the reference method were –1.1;15.4, 6.0;19.7 and 4.0;46.8 mg/dL for the hypoglycemic, euglycemic, and hyperglycemic ranges respectively. The percentage of overestimated glucose readings was higher than the underestimate values at normal (54% versus 44%) and high (59% versus 40%) glucose concentrations; conversely, in the hypoglycemic range, compared to the overestimated readings, the underestimated readings were higher (69% versus 31%).

Considering the ISO 15197:2013 requirements for FGMS when compared with the hexokinase method, 68% of values of total measurement are within the limits (Fig 3A); however, for PBGM compared with the hexokinase method, 72% of measurements are within the limits (Fig 3B).

Regarding the Consensus EGA, considering all the samples, with FGMS the 99% of the samples fall in the zone A+B. Considering the three subgroups in the hypoglycemic range only the 93% of the samples fall in zone A+B, in the euglycemic range 99% of the values fall in zone A+B, and in the hyperglycemic range 99% of samples fall in zone A+B. Considering the accuracy over time, we found a significant decrease of the mean difference (mg/dL) of glucose concentrations during the wearing period. Such difference was significant between the 1st–2nd (12.54 mg/dL) and the 6–7th (10.36 mg/dL) days ($P < .05$), and between the 6–7th (10.36 mg/dL) and 13–14th (14.07 mg/dL) days ($P < .05$). Considering only the last time period, a decrease of the mean difference was found in dogs with mild inflammation when compared with dogs without inflammation (–34.39 mg/dL versus 11.42 mg/dL) at the end of the study period.

Discussion

The use of the FGMS resulted in the accurate measurement of IG in diabetic dogs.

The utilization of FGMS is new in human diabetic patients and a single study is available.¹⁵ In this study, the IG measurements with the FGMS system were accurate compared with capillary BG reference values with accuracy remaining stable over 14 days of wearable technology and unaffected by patient characteristics.¹⁵

The application of the sensor on the neck of dogs was quick, simple, painless, and intuitive because of the applicator provided within the device package. The site of the positioning of the sensor on the neck was chosen for convenience, because it was easy to secure with a bandage on the body of the dog. After application, the sensor has 1-hour period of initialization and in all dog the sensor read the IG concentrations after 60 minutes from application as reported by the manufacturer. At the end of the wearing period, in 5/10 dogs a mild erythema was noted at the site of the application of the sensor and 1 dog had bent needle, but all dogs tolerated well the use of a bandage. The presence of mild erythema probably could be related to the removal of the

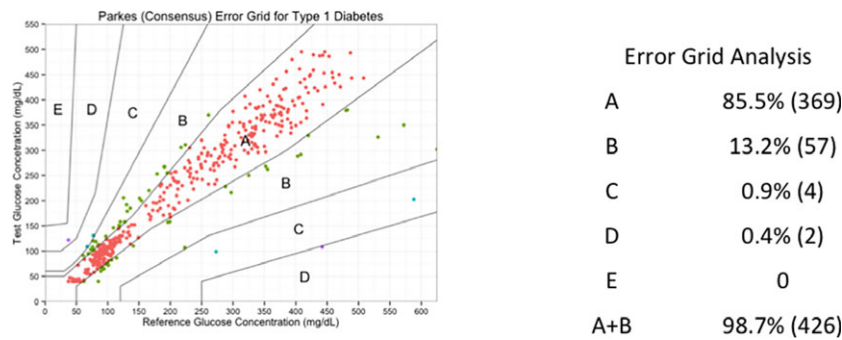


Fig 4. Parkes Consensus error grid analysis for the values obtained by FGMS and the representation with the percentage of values within A+B zones. The reference glucose values on the x-axis are plotted against the blood glucose by the glucose meter (y-axis). The different zones designate the magnitude of risk derived from the determination: no effect on clinical action (zone A), altered clinical action: little or no effect on clinical outcome (zone B), altered clinical action: likely to affect clinical outcome (zone C), altered clinical action: could have significant medical risk (zone D), and altered clinical action could have dangerous consequences (zone E) (Parkes et al.¹⁴).

patch that surrounds the sensor. In all dogs, the mild erythema disappeared spontaneously after 24 hours from the detachment of the sensor. Similar skin lesions were observed in human diabetic patients and there was moderate to severe itching in 0.5% of the cases and moderate erythema in 4% of cases.¹⁵ In one case, there was bent needle and this could be related to individual attitude of the dog or a deficiency to secure the sensor at the body of the dog.

In Davison² et al, a good correlation between the IG and PG was found with $R = 0.81$; however, in our study we found a correlation of $\rho = 0.94$. The correlations were lower considering the samples in the hypoglycemic, euglycemic, and hyperglycemic ranges, respectively; this was an expected occurrence because of a smaller sample size in each subgroup. The median individual correlation between IG and PG in each single dog decreased ($\rho = 0.85$), which could be related to the detachment of the sensor from the dog's skin or probably because of individual characteristics of the skin such as increasing thickness. It is possible that the skin thickness has an influence in the performance of the sensor. However, in the present study, only dogs without concurrent disorders such as hypothyroidism, hyperadrenocorticism, or pyoderma that could alter the thickness of the skin or the blood flow, were included.

In human medicine an increasing clinical accuracy for the system, FreeStyle Navigator was found for participants who had a body mass index (BMI) $>30 \text{ kg/m}^2$ compared to participants with BMI of $<25 \text{ kg/m}^2$. This finding has been attributed to differences in blood flow relative to subcutaneous adipose tissue thickness.¹⁶ Conversely, another recent study that evaluated the FGMS did not find any correlation with BMI.¹⁵

Flash glucose monitoring system is the unique among existing IG monitoring technologies in that the wired enzyme factory-calibrated sensor has a wear time of up to 14 days without additional calibrations.^{15,17} The results of our study evaluated an agreement between the FGMS and the reference method (hexokinase), which shows a minimal mean difference (2.3 mg/dL, SD 46.8) for the glucose readings. We compared the PG measured by the reference method and by a PBGM that

represents a glucometer approved for humans and recently evaluated as one of the best glucometers for dogs to obtain a further direct comparison between FGMS and PBGM.¹³ In our study, we found a mean difference of -21.2 mg/dL (SD 23.7) for PBGM compared to the reference method, which is in agreement with a previous study.¹³

The mean difference of IG compared with the reference method was minimal in the 3 subgroups, hypoglycemic, euglycemic, and hyperglycemic ranges. The results of the Consensus EGA showed acceptable clinical accuracy in the euglycemic and hyperglycemic ranges with 99% of reading fallen in zone A+B. In the hypoglycemic level, the clinical accuracy decreased slightly with 93% of readings in zone A+B.

During the wearing period, we found a significant decreased of the mean difference between 1st and 2nd days when compared to 13–14th days and between the 6–7th days compared to 13–14th days. This is in contrast with other studies that previously published as regards human diabetic patients where the accuracy of the CGMS decreased from the 1st day from application. This is due in part to the inflammatory responses to sensor insertion, which affect glucose concentrations in interstitial fluid.¹⁸ A decreased mean difference was found in the dogs with mild inflammation (-34.39 mg/dL versus 11.42 mg/dL) at the end of the wearing period, which could be related to the inflammation present at the site of application. Likewise, the presence of inflammation could affect the site of application.

Flash glucose monitoring system provides a broad and wide interval and numbers of readings during a 24-hour period and can be used to evaluate glucose patterns and trends. The hand-held reader displaces the previous 8-hour history but with a maximum upper range of 350 mg/dL . This range is appropriate for human diabetic patients where an intensive glycemic control is usually the goal of the treatment but not ideal in dogs where a wider range of glucose values is considered acceptable.

The limitations of the current study include that a single sensor was used in each dogs; therefore, the precision of the FGMS was not investigated. The time of

delay between the IG and PG is usually investigated by injecting a bolus of dextrose IV and then subsequently measuring the IG and PG in the subsequent minutes. This procedure was performed on some of the dogs in our study (data not showed), but FGMS was unable to measure the rapid changes between the PG and IG. Another limitation is that the thickness of the skin at the site of application of the sensor has not been evaluated.

The novel FGMS was accurate to evaluate IG when compared to the reference method. Flash glucose monitoring system could be a valid alternative for glucose monitoring in diabetic dogs because it has a small and comfortable sensor, allows for easy and quick glucose monitoring, calibrations are requested during the wearing period, and the sensor lasts up to 14 days.

Despite the ISO 2013 requirements were partially unfulfilled in our study, FGMS seems accurate to evaluate the PG in diabetic dogs with less clinical accuracy in the hypoglycemic range. Further studies are necessary to evaluate the clinical use of FGMS in the long-term monitoring of diabetic dogs and especially its ability to detect hypoglycemic events and the Somogyi phenomena.

Footnotes

^a FreeStyle Libre, Abbott, UK

^b Caninsulin, Intervet International BV, Boxmeer, The Netherlands

^c Lantus, Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

^d Humulin I, Eli Lilly Italia S.p.A., 50019 Sesto Fiorentino (FI) - Italia

^e AU400; Beckman-Coulter/Olympus, O'Callaghan's Mills, Ireland

^f Glucose OSR 6121; Beckman-Coulter/Olympus

^g Accu-check Aviva Nano, Roche Diagnostics S.p.A., Monza (MI), Italy

^h BSI Standards Publication, In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus (EN ISO 15197:2013).

ⁱ Prism version 5.0d, GraphPad software Inc, San Diego, CA

^j R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.